SPECIFICATION

COOLING DEVICE FOR BIOLOGICAL SAMPLES

The invention relates to a cooling equipment for biological samples, especially for the analysis, manipulation and processing of cryosamples, in accordance with the preamble of Claim 1.

The freezing of samples of biological material at temperatures of liquid nitrogen while preserving the vitality of the sample material is known in the area of biology, pharmacology, medicine and biotechnology. Such samples are also designated as cryosamples, the vitality-preserving storage of such cryosamples taking place in so-called cryotanks in which liquid nitrogen is present. In order to manipulate, process or investigate the cryosamples, they are removed from the cryotank and introduced into a cooling equipment that can consist, e.g., of a vat on whose bottom liquid nitrogen is present, that is also designated as a nitrogen lake, and that slowly evaporates, so that the cryosample in the vat continues to be sufficiently cooled. In order to avoid an outgassing of the liquid nitrogen into the ambient air, a transparent protective bell can be placed on the vat, whereby glove sleeves can be present in the wall of the protective bell through which an operator can manipulate the cryosample present in the vat.

The known cooling equipment described above for manipulating, processing or investigating cryosamples has the disadvantages of an unsatisfactory temperature constancy and temperature distribution inside the vat.

Another disadvantage of the known cooling equipment is the fact that the protective bell can mist over on account of the nitrogen outgassing from the nitrogen lake, which significantly hampers the visual monitoring.

In addition, in the known cooling equipment the temperature inside the vat cannot be adjusted or can only be adjusted with difficulty by changing the amount of liquid nitrogen introduced into the vat.

The invention therefore has the basic task of appropriately improving the initially described cooling equipment.

Another object can be to improve the temperature constancy in the cooling equipment, to make it possible to adjust the temperature, to optimize the distribution of temperature inside the cooling equipment, to prevent a misting over of the protective bell, and to minimize the moisture in the cooling space.

The above-cited task is solved by a cooling equipment in accordance with Claim 1.

The invention is based on the technical recognition that the unsatisfactory temperature constancy and temperature distribution inside the cooling vat is caused in the known cooling equipment by the fact that the nitrogen outgassing from the nitrogen lake spreads in an undefined manner inside the cooling equipment so that the desired operating temperature can only be achieved with difficulty and can hardly be controlled. Moreover, the uncontrolled outgassing of nitrogen from the nitrogen lake results in a misting over of the superposed protective bell.

The invention therefore comprises the general technical teaching of avoiding a nitrogen lake in the cooling equipment and instead introducing gaseous nitrogen in a controlled manner into the cooling space.

The cooling equipment according to the invention therefore has a cooling space for receiving cooled material, which cooling space is limited by an inner wall and an outer wall, an intermediate space being present between the inner wall and the outer wall into which a cooling agent supply line empties. The cooling agent (e.g., liquid nitrogen) is thus not introduced directly into the cooling space here but rather into the intermediate space between the inner wall and the outer wall of the cooling space, the inner wall being permeable for the cooling agent so that the cooling agent enters from the intermediate space between the outer wall and the inner wall through the inner wall into the cooling space.

A buffer material is preferably arranged in the intermediate space between the inner wall and the outer wall of the cooling space, which temporarily receives the cooling agent introduced into the intermediate space and continuously transfers it through the inner wall into the cooling space.

The buffer material is therefore preferably porous in order to be able to intermediately store, e.g., liquid nitrogen.

The outer wall of the cooling space is preferably impermeable to the cooling agent, in contrast to the inner wall of the cooling space, in order to prevent an exiting of the cooling agent out into the environment. Furthermore, the outer wall is preferably thermally insulating in order to avoid a cooling off of the environment and/or a warming up of the cooling equipment.

In contrast thereto, the inner wall of the cooling space preferably consists of a thermally conductive material such as, e.g., metal in order to improve the transfer of heat from the inner cooling space onto the cooling agent located in the intermediate space. Furthermore, it is advantageous if the material of the inner wall not only has a good thermal conductivity but also a high specific thermal capacity so that the inner wall counteracts undesired fluctuations of temperature with its thermal capacity as a thermal buffer.

In a preferred embodiment of the invention the inner wall is substantially grid-shaped so that the cooling agent located in the intermediate space can outgas into the cooling space without substantial hindrance.

Furthermore, in a preferred embodiment of the invention the cooling space is shaped like a vat and has a circumferential edge on its upper side, the cooling agent supply line preferably comprising a cooling agent distributor that extends along the circumferential edge of the cooling space and introduces the cooling agent, distributed over its length, into the intermediate space between the inner wall and the outer wall of the cooling space. Thus, the cooling agent is uniformly introduced into the intermediate space between the inner wall in the outer wall of the cooling space here, which advantageously results in a uniform distribution of temperature in the cooling space since the cooling space is uniformly cooled from all sides.

In addition, there is the possibility within the context of the invention that a heating element is arranged in the cooling space in order to heat the cooling space or to thaw the cooled material present in the cooling space. This

heating element is preferably arranged under or in a heating plate, preferably comprising several passages that allow a circulation of gas.

As in the above described, known cooling equipment, the cooling equipment in accordance with the invention also has the possibility of placing a removable protective bell onto the cooling space in order to prevent the penetration of moisture into the cooling space. This protective bell is preferably at least partially transparent in order to make possible a visible monitoring of the cooled material present in the cooling space.

In a preferred embodiment of the invention the protective bell has a sample lock through which the cooled material can be introduced into and removed from the cooling space, the sample lock preventing a thermal exchange with the environment to a large extent.

Furthermore, a cold-gas outlet can be arranged on the lower side of the protective bell and/or on the upper side of the cooling space via which outlet cooling agent or cold gas can escape from the cooling space. This cold-gas outlet generates a large temperature gradient at the level of the cold-gas outlet, the temperature above the cold-gas outlet being substantially higher than below the cold-gas outlet. This advantageously prevents a misting over of the protective bell.

Furthermore, a regulation of the temperature in the cooling space preferably takes place within the context of the invention. To this end, the cooling equipment of the invention preferably has a temperature sensor arranged in the cooling space in order to measure and/or regulate the

temperature in the cooling space. A controllable cooling agent valve that adjusts the amount of the supplied cooling agent and/or the cooling agent flow is then preferably provided as a actuator for temperature adjustment. The actual temperature control then takes place by a temperature control device that is connected on the input side to the temperature sensor and controls the cooling agent valve on the output side in accordance with a given theoretical temperature value.

The control of the cooling agent valve by the temperature control device can take place via a pulse generator that alternately opens and closes the temperature control device, the opening and closing times of the cooling agent valve being set by the pulse generator and adjusted by the temperature control device. The supply of cooling agent therefore takes place in a discontinuous manner in this instance in that the cooling agent valve alternately opens and closes.

The temperature sensor for detecting the temperature in the cooling space is preferably arranged at the processing position of the cooling space here, in order to measure and/or control the optimal processing temperature in the cooling space.

The temperature control device therefore preferably controls the temperature in the cooling space in such a manner that no cooling agent lake forms on the bottom of the cooling space.

Furthermore, it should also be mentioned that the cooling agent is preferably liquid nitrogen; the invention is, however, not limited to nitrogen as cooling agent but it can also be realized with other liquid or gaseous cooling agents

that can be introduced into the intermediate space between the inner wall and the outer wall of the cooling space.

The cooling equipment in accordance with the invention can be used for different temperature ranges such as, e.g., at temperatures of approximately -15°C, -130°C, -80°C, -40°C, +4C or +37°C, where the previously cited temperature ranges can have, e.g., a bandwidth of ±10°C, ±5°C or ±2°C. A temperature of 37°C is advantageous because the growth temperature of biological cells is then optimal. On the other hand, a temperature of +4°C has the advantage that the physiological processes in the cells are slowed down. During a manipulation of cells at a temperature of less than 4°C, there is less cell damage (e.g., with Tropsia and DMSO).

Finally, the invention has not only the previously described cooling equipment as a device, but also the use of such a cooling equipment for investigating, processing and/or manipulating a cryosample.

Other advantageous further developments of the invention are characterized in the subclaims or are explained in detail below together with a description of the preferred embodiment of the invention using the figures.

Figure 1 shows a perspective view of a preferred embodiment of the cooling equipment in accordance with the invention with a superposed protective bell.

Figure 2 shows a perspective view of the protective bell of figure 1 in its removed state.

Figure 3 shows a cross-sectional view of the wall structure of the cooling space in the cooling equipment of figure 1.

Figure 4 shows a simplified perspective view of the cooling agent supply in the cooling equipment of figure 1 and

Figure 5 shows a control-technology equivalent circuit diagram of the cooling equipment of figure 1.

The embodiment of a cooling equipment 1 in accordance with the invention and shown in the drawings serves to control the temperature of a cooling space for receiving cryosamples during an analysis, manipulation and/or processing.

To this end cooling equipment 1 has cryovat 2 with a vat-shaped cooling space 3 open at the top, a removable protective bell 4 being placed on cryovat 2, which protective bell prevents the penetration of moisture from the environment into the cooling space and is shown in detail in figure 2.

Protective bell 4 has sample lock 5 for introducing the cryosamples into cooling space 3 and for removing the cryosamples from cooling space 3, which lock is attached to the side of protective bell 4 and prevents a thermal exchange with the environment to a great extent during the introduction and/or removal of the cryosamples and minimizes the moisture in cooling space 3.

Furthermore, protective bell 4 has light 6 on its upper side in order to illuminate cooling space 3 and thus facilitate the manipulation of cryosamples present in cooling space 3.

The protective bell 4 itself consists here of a transparent material, which permits a simple visual monitoring by an operator.

Two conventional glove sleeves 7, 8 are located on the beveled front side of protective bell 4 through which an operator can manipulate the cryosamples present in cooling space 3 without gas exchange.

Furthermore, two openings 9 are located on the back side of protective bell 4 through which the cold gas can exit from protective bell 4. The two openings 9 result in have the consequence that a large temperature gradient is formed at the level of the two openings 9 since cold gas escapes to the outside from the two openings 9. The atmosphere in protective bell 4 above openings 9 is therefore substantially warmer than below openings 9, which counteracts a misting over of the inner walls of protective bell 4.

Furthermore a control and display panel 10 on which the temperature in cooling space 3 can be displayed and adjusted is located on the front of cryovat 2.

The cooling of cooling space 3 takes place here by liquid nitrogen supplied from a nitrogen tank (e.g., an Apollo container) via nitrogen line 11, nitrogen line 11 not directly emptying into cooling space 3 in order to avoid the formation of a nitrogen lake on the bottom of cooling space 3. Instead, nitrogen line 11 empties via an electrically controllable cooling agent valve 12 into cooling agent supply line 13, the cooling agent supply line 13 extending along the circumferential edge of vat-shaped cooling space 3 and

transferring the liquid nitrogen over its length in a distributed manner.

Here, cooling space 3 is delimited by grid-shaped inner wall 14 consisting of metal which is and surrounded by outer wall 15, inner wall 14 and outer wall 15 enclosing an intermediate space in which buffer material 16 is arranged. Cooling agent supply line 13 is arranged in a lateral direction between inner wall 14 and outer wall 15 above buffer material 16 and has downwardly directed exit openings through which liquid nitrogen is transferred from the interior of cooling agent supply line 13 into buffer material 16. Buffer material 16 absorbs the liquid nitrogen and transfers it continuously through grid-shaped inner wall 14 into cooling space 3.

Cooling agent valve 13 operates discontinuously here in that the cooling agent valve 13 either opens or closes.

Cooling agent valve 12 is controlled here by pulse generator 17, the opening time T_{AUF} and the closing time T_{ZU} for cooling agent valve 12 being given by controller 18 for dosing the cooling agent.

This regulation takes place as a function of the temperature in cooling space 3 that is measured by temperature sensor 19, the temperature sensor 19 being arranged at the processing position of cooling space 3.

Therefore, a temperature sensor 19 measures a temperature T_{IST} [IST = ACTUAL] and passes it on to subtractor 20 that receives a theoretical value T_{SOLL} for the temperature in cooling space 3 as another input variable and calculates a theoretical-actual deviation ΔT.

Controller 18 then adjusts the opening time T_{AUF} and the closing time T_{ZU} for cooling agent valve 12 in such a manner that the desired temperature (e.g., -130°C) prevails in cooling space 3 without a nitrogen lake forming on the bottom of cooling space 13.

In addition, a heating plate 21 is arranged on the bottom of cooling space 3 that makes it possible to heat the cryosample and cooling space 3.

Numerous vertical through passages 22 that make a circulation of gas possible are arranged in heating plate 21.

The invention is not limited to the previously described embodiment but rather a plurality of variants and modifications are possible that also make use of the concept of the invention and therefore fall within its scope of protection.

List of reference signs:

1 Cooling equipment
2 Cryovat
3 Cooling area
4 Protective bell
5 Sample lock
6 Light
7, 8 Glove Sleeves
9 Openings
10 Control and display panel
11 Nitrogen line
12 Cooling agent valve
13 Cooling agent supply line
14 Inner wall
15 Outer wall
16 Buffer material
17 Pulse generator
18 Controller
19 Temperature sensor
20 Subtractor
21 Heating plate
22 Passages